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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,400	06/20/2001	Dennis Murphy	DIVER1120-4	4902
20985	7590	12/19/2003	EXAMINER RAMIREZ, DELIA M	
FISH & RICHARDSON, PC 12390 EL CAMINO REAL SAN DIEGO, CA 92130-2081			ART UNIT 1652	PAPER NUMBER
DATE MAILED: 12/19/2003				

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/886,400

Applicant(s)

MURPHY ET AL.

Examiner

Delia M. Ramirez

Art Unit

1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 29 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 93-137 is/are pending in the application.
- 4a) Of the above claim(s) 133-137 is/are withdrawn from consideration.
- 5) ☐ Claim(s) 104 is/are allowed.
- 6) ☒ Claim(s) 93-103 and 105-132 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 29 September 2003 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 13) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
- a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 9/29/03.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 93-137 are pending.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/29/2003 has been entered.

Applicant's amendment of claims 93-119, addition of claims 120-137, and a declaration under 37 CFR 1.132 by Dr. Jay Short, in a communication filed on 9/29/2003, are acknowledged.

It is noted that newly added claims 133-137 will not be examined in the instant application in view of the fact that these claims are not drawn to the elected invention, i.e. the polypeptide of SEQ ID NO: 4 (Group II). The instant claims are drawn to a method of expressing the nucleic acid encoding the polypeptide of SEQ ID NO: 4. As indicated in the restriction requirement mailed on 2/27/2002, such method was included in non-elected Group I. Claims 133-137 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Information Disclosure Statement

1. The information disclosure statement (IDS) submitted on 9/29/2003 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Drawings

2. The submission of corrected Figure 5A on 9/25/2003 is acknowledged. The corrected figure is accepted by the Examiner.

Claim Objections

3. Claim 130 is objected to due to the following informalities. For clarity, it is suggested that the term “wherein arginine is substituted for lysine or glutamic acid is substituted for aspartic acid or glutamine is substituted for asparagine” be replaced with “wherein arginine is substituted for lysine, glutamic acid is substituted for aspartic acid, or glutamine is substituted for asparagine”. Appropriate correction is required.

Claim Rejections - 35 USC § 112, Second Paragraph

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:
- The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.
5. Claims 93-103, 105-128, 131-132 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.
6. Claims 93, 95-103, 116, 117, 121-128 (claims 94, 105-115, 118-120, 131-132 dependent thereon) are indefinite in the recitation of “at least about” because it renders the claims vague and confusing. Applicants traverse this rejection on the grounds that the term “about” is a descriptive term commonly used in patent claims. This argument is not found persuasive. Even if the term “about” is deemed definite, the combination of the terms “at least” and “about” is not. As indicated previously in Paper No. 19, mailed on 3/26/2003, the use of this language is contradictory because the term “about” can be interpreted as “less than” whereas the term “at least” is synonym of “no less than”. As such, the term is

deemed indefinite. For examination purposes, it will be assumed that the term reads “at least”.

Correction is required.

7. Claims 96-103 are indefinite in the recitation of “an isolated or recombinant polypeptide.....having....sequence identity to a polypeptide...and having α -galactosidase activity” as it is unclear if the term “ α -galactosidase activity” refers to the claimed polypeptide or that of a polypeptide having the sequence as set forth in SEQ ID NO: 4”. For examination purposes it will be assumed that the term refers to the claimed polypeptide. Correction is required.

8. Claim 105 (claims 106-115, 118-119, 131 dependent thereon) is indefinite in the recitation of “an isolated or recombinant polypeptide comprising at leastof the polypeptide of claim 93 or claim 94 and having α -galactosidase activity” as it is unclear if the term “ α -galactosidase activity” refers to the activity of the claimed polypeptide or the activity of the polypeptides of claim 93 or 104. For examination purposes, it will be assumed that the term refers to the activity of the polypeptide of claim 93 or claim 104. Correction is required.

9. Claims 106-115 are indefinite in the recitation of “polypeptide of claim X comprising at least Y consecutive amino acids of the polypeptide.” as it is unclear which polypeptide is being referred to by the term “of the polypeptide”. For examination purposes, it will be assumed that the meaning of the term “of the polypeptide” is “of the polypeptide of claim 93 or claim 104”. Correction is required.

10. Claims 116-117, 121-128 (claim 120 dependent thereon) are indefinite in the recitation of “polypeptide encoded by a sequence having at least about X% sequence identity to SEQ ID NO: 3” for the following reasons. As known in the art, polynucleotides encode polypeptides, and sequences are graphical representations of the order in which nucleotides/amino acids are arranged in a molecule. Therefore, it is unclear as to how a polypeptide is encoded by a sequence. For examination purposes, it will be assumed that the term reads “polypeptide encoded by a polynucleotide having ...sequence identity to SEQ ID NO: 3”. Correction is required.

Art Unit: 1652

11. Claims 121-128, 130-131 are indefinite in the recitation of “isolated or recombinant of claim X” as it is unclear what is being claimed. It is suggested that the term be amended to recite “isolated or recombinant polypeptide of claim X”. For examination purposes, the suggested language will be used. Correction is required.

12. Claim 131 is indefinite in the recitation of “polypeptide is associated with a polyethylene glycol” as it is unclear and confusing. As written, it is unclear if the “association” refers to chemical linkage of the claimed polypeptide to polyethylene glycol or if the “association” refers to an undefined relationship between the claimed polynucleotide and polyethylene glycol. For examination purposes, it will be assumed that the claim is directed to the polypeptide of claim 93 or claim 105 wherein the polypeptide is chemically linked to polyethylene glycol. Correction is required.

13. Claim 132 is indefinite in the recitation of “polypeptide comprising an active fragment of the polypeptide of claim 93 or claim 104” as it is unclear what the meaning of the term “active fragment” is within the context of the claim. As written, one cannot determine if the term “active” refers to “ α -galactosidase activity” or if another “activity” is being implied. For examination purposes, no patentable weight will be given to the term. Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

14. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 105-115 remain rejected and claims 118-119 (amended), 129-132 (new) are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to

reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

16. This rejection, which was applied to claims 105-115 in Paper No. 19, mailed on 3/26/2003, is maintained on amended claims 105-115 and is now applied to amended claims 118-119 as well as newly added claims 129-132 for the reasons of record and those set forth below.

17. Applicants argue in view of the amendments made to the claims, claims 105-115 are directed to active fragments of a polypeptide of the invention. Applicants maintain that only the claimed sequence need be described in the specification to satisfy the written description requirement and that those polypeptides having an additional structural features due to the use of open language need not be described in the specification. Applicants refer to Example 14 of the USPTO Written Description Guidelines as shown in Exhibit A and assert that the instant claims recite polypeptides which are defined by structure and function. Applicants further submit that the claims fully comply with the written description requirements as set forth in *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1398 (Fed. Cir. 1997) and conclude that those of skill in the art would recognize Applicant's possession of the claimed invention, citing *Vas-cath Inc. V. Mahukar*, 19 USPQ2d 1 111, (Fed Cir. 1991). Applicants further submit that the disclosed function, i.e. α -galactosidase, is sufficiently correlated to a particular known structure, i.e. the polypeptide of SEQ ID NO: 4, and a physical property (i.e. % sequence identity).

18. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection as it relates to claims 105-115 or to avoid the rejection of claims 118-119, 129-132. It is noted that the claims 105-115 as amended do not recite a functional limitation for the claimed polypeptides. In addition, there is no functional limitation regarding claims 118-119, 131-132. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation. As such, claims 105-115, 118-119, 131-132 are directed to a genus of polypeptides of any function comprising fragments of

the polypeptide of SEQ ID NO: 4 or an α -galactosidase having at least 50% sequence identity to the polypeptide of SEQ ID NO: 4. Since no functional limitation is recited in claims 129-130, the instant claims are directed to a genus of polypeptides of any function having the amino acid sequence of SEQ ID NO: 4 with any number of conservative substitutions, wherein said conservative substitutions comprise substituting one hydrophobic amino acid for another, one polar amino acid for another, arginine residues for lysine residues, glutamic acid residues for aspartic acid residues, or glutamine residues for asparagines residues.

While the specification discloses the structure of the α -galactosidase of SEQ ID NO: 4, the specification is completely silent in regard to (1) the functions of all the genera of polypeptides encompassed by the claims, (2) which fragments of 10-150 amino acids of the polypeptide of SEQ ID NO: 4 are required for α -galactosidase function, (3) which fragments of 10-150 amino acids of an α -galactosidase having at least 50% sequence identity to the polypeptide of SEQ ID NO: 4 are required for α -galactosidase function, (4) which fragments of an α -galactosidase having 50% sequence identity to the polypeptide of SEQ ID NO: 4 have enzymatic activity, or (5) which amino acids in the polypeptide of SEQ ID NO: 4 can be conservatively substituted as recited and still retain α -galactosidase activity. Furthermore, since the claims are not limited as to how many conservative substitutions a polypeptide having α -galactosidase activity can have, the claims encompass an extremely large number of possible substitution combinations ($2^N - 1$ where $N=364$) and the specification provides no clue as to which of these combinations would result in a polypeptide retaining α -galactosidase activity. Thus, the claims encompass genera of polypeptides of substantial variability in regard to function and structure.

As indicated previously and reiterated herein, a sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. Even if one assumes that the claimed polypeptides

Art Unit: 1652

are limited in regard to function, i.e. α -galactosidases, each of the recited structural features of the genera of polypeptides claimed (i.e. (1) 10-150 contiguous amino acids of the polypeptide of SEQ ID NO: 4 or an α -galactosidase having 50% sequence identity to the polypeptide of SEQ ID NO: 4, (2) any fragment of the polypeptide of SEQ ID NO: 4 or an α -galactosidase having 50% sequence identity to the polypeptide of SEQ ID NO: 4, and (3) the sequence of SEQ ID NO: 4 with any number of conservative substitutions), does not constitute a substantial portion of the genus as the remainder of the structure of any polypeptide having α -galactosidase activity is completely undefined and the specification does not define the remaining structural features necessary for members of the genus to be selected. The specification discloses only a single species of the genera of polypeptides (i.e., the polypeptide of SEQ ID NO: 4) claimed, which is insufficient to put one of skill in the art in possession of the attributes and features of the claimed invention. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

19. Claims 93-102, 105-119 remain rejected and newly added claims 120-127, 129-132 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polypeptide of SEQ ID NO: 4, and a composition comprising the polypeptide of SEQ ID NO: 4, does not reasonably provide enablement for (1) α -galactosidases having at least 50%-90% sequence identity to the polypeptide of SEQ ID NO: 4, (2) polypeptides of any function comprising at least 10-150 consecutive amino acids of the polypeptide of SEQ ID NO: 4, (3) polypeptides of any function comprising at least 10-150 consecutive amino acids of an α -galactosidase having at least 50% sequence identity to the polypeptide of SEQ ID NO: 4, (4) compositions comprising (1), (2) or (3), (5) any enzyme capable of hydrolyzing any saccharide wherein said enzyme is encoded by a polynucleotide at least 50% sequence identical to that of SEQ ID NO: 3, (6) α -galactosidases encoded by polynucleotides having at least 50% - 85% sequence identity to the polynucleotide of SEQ ID NO: 3, (7) α -galactosidases of (6) capable of

Art Unit: 1652

renaturing and regaining activity after exposure to 60-105 °C, (8) polypeptides of any function having a sequence as set forth in SEQ ID NO: 4 except that any number of conservative substitutions are allowed, (9) polypeptides of any function comprising any fragment of (1) or the polypeptide of SEQ ID NO: 4, or (10) the polypeptide of (1) chemically linked to polyethylene glycol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

20. This rejection, which was discussed at length in Paper No. 19, mailed on 3/26/2003, is applied to amended claims 93-102, 105-119 and newly added claims 120-127, 129-132 for the reasons of record and those set forth below.

21. Applicants argue that the specification enabled the skilled artisan at the time of the invention to identify, make and use a genus of α -galactosidases of the invention. Applicants refer to a declaration by inventor Jay Short, who declares that the state of the art at the time of the invention and the level of skill of the person of ordinary skill in the art was very high. Dr Short's declaration further states that one of skill in the art at the time of the invention could use the teachings of the specification and other protocols known in the art to screen for polypeptides having α -galactosidase activity and that while the number of samples needed to be screened may have been high, the screening procedures were routine and successful results predictable. According to Dr. Short's declaration, knowledge of the specific structural elements which correlate with α -galactosidase activity would not have been required to create variants and test them for activity. Applicants further argue that enablement is not precluded by the necessity to screen large number of compositions as long as that screening is routine. Applicants refer to *Hybritech, Inc. v. Monoclonal Antibodies, Inc.* as support for the argument that the claimed invention is enabled even if there is a need to screen numbers of negatives to find a sample with the desired activity.

22. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection as it relates to amended claims 93-102, 105-119 and newly added claims 120-127, 129-132.

Art Unit: 1652

The instant claims are directed to (1) α -galactosidases having at least 50%-90% sequence identity to the polypeptide of SEQ ID NO: 4, (2) polypeptides of any function comprising at least 10-150 consecutive amino acids of the polypeptide of SEQ ID NO: 4, (3) polypeptides of any function comprising at least 10-150 consecutive amino acids of an α -galactosidase having at least 50% sequence identity to the polypeptide of SEQ ID NO: 4, (4) compositions comprising (1), (2) or (3), (5) any enzyme capable of hydrolyzing any saccharide wherein said enzyme is encoded by a polynucleotide at least 50% sequence identical to that of SEQ ID NO: 3, (6) α -galactosidases encoded by polynucleotides having at least 50% - 85% sequence identity to the polynucleotide of SEQ ID NO: 3, (7) α -galactosidases of (6) capable of renaturing and regaining activity after exposure to 60-105 °C, (8) polypeptides of any function having a sequence as set forth in SEQ ID NO: 4 except that any number of conservative substitutions are allowed, (9) polypeptides of any function comprising any fragment of (1) or the polypeptide of SEQ ID NO: 4, or (10) the polypeptide of (1) chemically linked to polyethylene glycol. The scope of the claims is not commensurate with the enablement provided in view of the extremely large number of polypeptides of any function encompassed by the claims as well as the lack of knowledge in regard to the correlation between α -galactosidase activity and structure, such that one of skill in the art would reasonably conclude that the disclosure is enabling for the full scope of the claims.

As indicated in the Final Action mailed on 3/26/2003 and reiterated herein, the specification is completely silent in regard to which are the amino acid residues which can be substituted, deleted, or inserted in the polypeptide of SEQ ID NO: 4 to obtain structural homologs of the polypeptide of SEQ ID NO: 4 as recited in the claims which retain α -galactosidase activity. In addition, the specification does not provide any clue as to which 10-150 consecutive amino acid fragments of the polypeptide of SEQ ID NO: 4 are required to display α -galactosidase activity nor does it provide any clue as to which fragments of an α -galactosidase having at least 50% sequence identity to the polypeptide of SEQ ID NO: 4 are essential for α -galactosidase activity. Moreover, no teaching or suggestion has been presented in regard

Art Unit: 1652

to the critical structural elements required in a polypeptide to catalyze the enzymatic hydrolysis of any saccharide or the critical structural elements in an α -galactosidase encoded by a nucleic acid having 50% sequence identity to SEQ ID NO: 3 such that the α -galactosidase has thermal stability at 60-105 C. The art as evidenced by Bork, Broun et al., Van de Loo et al., Witkowski et al. and Seffernick et al., clearly teaches the unpredictability of assigning function based on structural homology and how small structural changes can lead to major changes in function. Therefore, in the absence of any information as to how structure correlates with function, one of skill in the art would have to go through the burden of undue experimentation to isolate/make the polypeptides as encompassed by the claims, to practice the full scope of the claimed method.

The Examiner acknowledges the ruling in *Hybritech, Inc. v. Monoclonal Antibodies, Inc* as well as the declaration by inventor Jay Short, and agrees that enablement is not precluded by the need of screening a number of compositions as long as the screening is routine. Furthermore, the Examiner agrees that creation of variants having the structural limitations recited in the claims is routine in the art. However, the Examiner disagrees with Applicant's contention that testing the extremely large number of variants encompassed by the claims is not undue experimentation when there is no guidance or knowledge as to which are the structural elements in the polypeptide of SEQ ID NO: 4 that correlate with enzymatic hydrolysis of any saccharide, α -galactosidase activity or thermal stability at 60-105 C. It is not routine in the art to randomly create an infinite number of variants and test them for activity. Instead, as indicated above, one of skill in the art would have some knowledge or guidance as to how structure correlates with function such that a reasonable number of variants with the potentiality of having the desired function can be created and tested. Thus, in view of the information provided, the lack of relevant examples, the lack of knowledge about the critical structural elements required for enzymatic hydrolysis of any saccharide, α -galactosidase activity or thermal stability, and the unpredictability of the art in

Art Unit: 1652

regard to accurate annotation of function based on structural homology, one of skill in the art cannot reasonably conclude that the specification is enabling for the full scope of the claimed invention.

Allowable Subject Matter

23. Claim 104 appears to be allowable over the prior art of record.

Conclusion

24. Certain papers related to this application may be submitted to Art Unit 1652 by facsimile transmission. The FAX number is (703) 308-4556. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If Applicant submits a paper by FAX, the original copy should be retained by Applicant or Applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (703) 306-0288. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (703) 308-3804. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
December 11, 2003


